CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074711

Trade Name : MEXILETINE HCL CAPSULES

Generic Name: Mexiletine Hcl Capsules USP

Sponsor : Watson Laboratories, Inc.

Approval Date: February 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074711

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074711

APPROVAL LETTER

ANDA 74-711

Watson Laboratories, Inc.
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, CA 91720

Dear Dr. Hsia:

This is in reference to your abbreviated new drug application dated July 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Mexiletine Hydrochloride Capsules USP, 150 mg, 200 mg, and 250 mg.

Reference is also made to your amendments dated February 6, 1996, January 7, and February 3, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Mexiletine Hydrochloride Capsules USP, 150 mg, 200 mg, and 250 mg, are bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Mexitil® Capsules, 150 mg, 200 mg, and 250 mg, respectively, of Boehringer Ingelheim Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

2/25/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074711

FINAL PRINTED LABELING

NDC 52544-492-01

MEXILETINE HYDROCHLORIDE CAPSULES, USP

200 mg

TAKE WITH FOOD OR ANTACID

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Each Capsule Contains:
Mexiletine Hydrochloride, USP ..... 200 mg

Dispense in a tight, light-resistant container as defined in the USP.

USUAL DOSAGE: Read accompanying prescribing information.

Store below 30°C (86°F).

TAKE WITH FOOD OR ANTACID

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-492-01 9

Lot No.:

Exp:

NDC 52544-492-05

MEXILETINE HYDROCHLORIDE CAPSULES, USP

200 mg

TAKE WITH FOOD OR ANTACID

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

Each Capsule Contains:
Mexiletine Hydrochloride, USP ..... 200 mg

Dispense in a tight, light-resistant container as defined in the USP.

USUAL DOSAGE: Read accompanying prescribing information.

Store below 30°C (86°F).

TAKE WITH FOOD OR ANTACID

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-492-05 7

Lot No.:

Exp:

NDC 52544-493-05

MEXILETINE HYDROCHLORIDE CAPSULES, USP

250 mg

TAKE WITH FOOD OR ANTACID

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

Each Capsule Contains:
Mexiletine Hydrochloride, USP ..... 250 mg

Dispense in a tight, light-resistant container as defined in the USP.

USUAL DOSAGE: Read accompanying prescribing information.

Store below 30°C (86°F).

TAKE WITH FOOD OR ANTACID

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-493-05 4

Lot No.:

Exp:

NDC 52544-491-01

MEXILETINE HYDROCHLORIDE CAPSULES, USP
150 mg

TAKE WITH FOOD OR ANTACID

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Each Capsule Contains:
Mexiletine Hydrochloride, USP ... 150 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: Read accompanying prescribing information.
Store below 30°C (86°F).
TAKE WITH FOOD OR ANTACID
Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-491-01 2

Lot No.:
Exp:

NDC 52544-491-05

MEXILETINE HYDROCHLORIDE CAPSULES, USP
150 mg

TAKE WITH FOOD OR ANTACID

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

Each Capsule Contains:
Mexiletine Hydrochloride, USP ..... 150 mg
Dispense in a tight, light-resistant container as defined in the USP.
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Store below 30°C (86°F).
TAKE WITH FOOD OR ANTACID
Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-491-05 0

Lot No.:
Exp:

NDC 52544-493-01

MEXILETINE HYDROCHLORIDE CAPSULES, USP
250 mg

TAKE WITH FOOD OR ANTACID

CAUTION: Federal law prohibits dispensing without prescription.

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Store below 30°C (86°F).
TAKE WITH FOOD OR ANTACID
Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-493-01 6

Lot No.:
Exp:

FEB 26

MEXILETINE HYDROCHLORIDE CAPSULES, USP

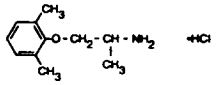
APPROVED

DESCRIPTION

Mexiletine hydrochloride is an orally active antiarrhythmic agent available as 150 mg, 200 mg and 250 mg capsules. 100 mg of mexiletine hydrochloride is equivalent to 83.31 mg of mexiletine base. It is a white to off-white crystalline powder with slightly bitter taste, freely soluble in water and in alcohol. Mexiletine hydrochloride has a pKa of 9.2.

Chemically, mexiletine hydrochloride is 1-methyl-2-(2, 6-xylyloxy) ethylamine hydrochloride. Its molecular formula is $C_{11}H_{17}NO{\cdot}HCl$ and molecular weight is 215.72.

Following is its structural formula:



Each capsule, for oral administration contains 150 mg, 200 mg, or 250 mg mexiletine hydrochloride. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, corn starch, D&C Red No. 28, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide. Mexiletine hydrochloride capsules 150 mg also contain black iron oxide, red iron oxide and yellow iron oxide. Mexiletine hydrochloride capsules 250 mg also contain FD&C Green No. 3.

CLINICAL PHARMACOLOGY

Mechanism of Action: Mexiletine hydrochloride is a local anesthetic, antiarrhythmic agent, structurally similar to lidocaine, but orally active. In animal studies, mexiletine has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by glycoside toxicity and coronary artery ligation. Mexiletine, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine decreased the effective refractory period (ERP) in Purkinje fibers. The decrease in ERP was of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.

Electrophysiology in Man: Mexiletine is a Class 1B antiarrhythmic compound with electrophysiologic properties in man similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide.

In patients with normal conduction systems, mexiletine has a minimal effect on cardiac impulse generation and propagation. In clinical trials, no development of second-degree or third-degree AV block was observed. Mexiletine did not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, mexiletine may be useful in the treatment of ventricular arrhythmias associated with a prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of mexiletine has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexiletine hydrochloride, at doses of 200 to 400 mg q8h, produced a significant reduction of ventricular premature beats, paired beats, and episodes of non-sustained ventricular tachycardia compared to placebo and was similar in effectiveness to the active agents. Among all patients entered into the studies, about 30% in each treatment group had a 70% or greater reduction in PVC count and about 40% failed to complete the 3 month studies because of adverse effects. Follow-up of patients from the controlled trials has demonstrated continued effectiveness of mexiletine in long-term use.

Hemodynamics: Hemodynamic studies in a limited number of patients, with normal or abnormal myocardial function, following oral administration of mexiletine hydrochloride, have shown small, usually not statistically significant, decreases in cardiac output and increases in systemic vascular resistance, but no significant negative inotropic effect. Blood pressure and pulse rate remain essentially unchanged. Mild depression of myocardial function, similar to that produced by lidocaine, has occasionally been observed following intravenous mexiletine hydrochloride therapy in patients with cardiac disease.

Pharmacokinetics: Mexiletine is well absorbed (~90%) from the gastrointestinal tract. Unlike lidocaine, its first-pass metabolism is low. Peak blood levels are reached in two to three hours. In normal subjects, the plasma elimination half-life of mexiletine is approximately 10 to 12 hours. It is 50 to 60% bound to plasma protein, with a volume of distribution of 5 to 7 liters/kg. Mexiletine is metabolized in the liver. Approximately 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion, while alkalinization retards it.

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus the therapeutic activity of mexiletine is due to the parent compound.

Hepatic impairment prolongs the elimination half-life of mexiletine. In eight patients with moderate to severe liver disease, the mean half-life was approximately 25 hours.

Consistent with the limited renal elimination of mexiletine, little change in the half-life has been detected in patients with reduced renal function. In eight patients with creatinine clearance less than 10 ml/min, the mean plasma elimination half-life was 15.7 hours; in seven patients with creatinine clearance between 11 to 40 ml/min, the mean half-life was 13.4 hours.

The absorption rate of mexiletine is reduced in clinical situations such as acute myocardial infarction in which gastric emptying time is increased. Narcotics, atropine and magnesium-aluminum hydroxide have also been reported to slow the absorption of mexiletine. Metoclopramide has been reported to accelerate absorption.

Mexiletine plasma levels of at least 0.5 mcg/ml are generally required for therapeutic response. An increase in the frequency of central nervous system adverse effects has been observed when plasma levels exceed 2 mcg/ml. Thus the therapeutic range is approximately 0.5 to 2 mcg/ml. Plasma levels within the therapeutic range can be attained with either three times daily or twice daily dosing but peak to trough differences are greater with the latter regimen, creating the possibility of adverse effects at peak and arrhythmic escape at trough. Nevertheless, some patients may be transferred successfully to the twice daily regimen. (See DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Mexiletine Hydrochloride Capsules are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of mexiletine, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of mexiletine treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Mexiletine hydrochloride is contraindicated in the presence of cardiogenic shock or pre-existing second- or third-degree AV block (if no pacemaker is present).

WARNINGS

Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of the CAST results to other populations (e.g. those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of mexiletine and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of mexiletine as well as other antiarrhythmic agents should be reversed for patients with life-threatening ventricular arrhythmia.

Acute Liver Injury: In postmarketing experience abnormal liver function tests have been reported, some in the first few weeks of therapy with mexiletine hydrochloride. Most of these have been observed in the setting of congestive heart failure or ischemia and their relationship to mexiletine has not been established.

PRECAUTIONS

General: If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with mexiletine if continuously monitored. A limited number of patients (45 of 475 in controlled clinical trials) with pre-existing first degree AV block were treated with mexiletine; none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics mexiletine hydrochloride can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia: (see ADVERSE REACTIONS), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or to exercise provocation, 10 to 15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexiletine should be used with caution in patients with hypotension and severe congestive heart failure because of the potential for aggravating these conditions.

Since mexiletine is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half-life of mexiletine, patients with liver disease should be followed carefully while receiving mexiletine. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during mexiletine hydrochloride therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of mexiletine.

SGOT Elevation and Liver Injury: In three-month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 1% of both mexiletine-treated and control patients. Approximately 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These elevations were often asymptomatic and transient, usually not associated with elevated bilirubin levels and usually did not require discontinuation of therapy. Marked elevations of SGOT (> 1000 U/L) were seen before death in four patients with end-stage cardiac disease (severe congestive heart failure, cardiogenic shock).

Rare instances of severe liver injury, including hepatic necrosis, have been reported in association with mexiletine treatment. It is recommended that patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction, be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, consideration should be given to discontinuing therapy.

Blood Dyscrasias: Among 10,867 patients treated with mexiletine in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm³) or agranulocytosis were seen in 0.06% and milder depressions of leukocytes were seen in 0.06%, and thrombocytopenia was observed in 0.16%. Many of these patients were seriously ill and receiving concomitant medications with known hematologic adverse effects. Rechallenge with mexiletine in several cases was negative. Marked leukopenia or agranulocytosis did not occur in any patient receiving mexiletine alone; five of the six cases of agranulocytosis were associated with procainamide (sustained release preparations in four) and one with vinblastine. If significant hematologic changes are observed, the patient should be carefully evaluated, and, if warranted, mexiletine should be discontinued. Blood counts usually return to normal within one month of discontinuation. (See ADVERSE REACTIONS).

Convulsions (seizures) did not occur in mexiletine controlled clinical trials. In the compassionate use program, convulsions were reported in about 2 of 1000 patients. Twenty-eight percent of these patients discontinued therapy. Convulsions were reported in patients with and without a prior history of seizures. Mexiletine should be used with caution in patients with known seizure disorder.

Drug Interactions: In a large compassionate use program mexiletine has been used concurrently with commonly employed antianginal, antihypertensive, and anticoagulant drugs without observed interactions. A variety of antiarrhythmics such as quinidine or propranolol were also added, sometimes with improved control of ventricular ectopy. When phenytoin or other hepatic enzyme inducers such as rifampin and phenobarbital have been taken concurrently with mexiletine, lowered mexiletine plasma levels have been reported. Monitoring of mexiletine plasma levels is recommended during such concurrent use to avoid ineffective therapy.

In a formal study, benzodiazepines were shown not to affect mexiletine plasma concentrations. ECG intervals (PR, QRS, and QT) were not affected by concurrent mexiletine and digoxin, diuretics, or propranolol.

Concurrent administration of cimetidine and mexiletine has been reported to increase, decrease, or leave unchanged mexiletine plasma levels; therefore patients should be followed carefully during concurrent therapy.

Mexiletine does not alter serum digoxin levels but magnesium-aluminum hydroxide, when used to treat gastrointestinal symptoms due to mexiletine, has been reported to lower serum digoxin levels.

Concurrent use of mexiletine and theophylline may lead to increased plasma theophylline levels. One controlled study in eight normal subjects showed a 72% mean increase (range 35 to 136%) in plasma theophylline levels. This increase was observed at the first test point which was the second day after starting mexiletine. Theophylline plasma levels returned to pre-mexiletine values within 48 hours after discontinuing mexiletine. If mexiletine and theophylline are to be used concurrently, theophylline blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in theophylline dose should be considered.

Additionally, in one controlled study in five normal subjects and seven patients, the clearance of caffeine was decreased 50% following the administration of mexiletine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of carcinogenesis in rats (24 months) and mice (18 months) did not demonstrate any tumorigenic potential. Mexiletine was found to be non-mutagenic in the Ames test. Mexiletine did not impair fertility in the rat.

Pregnancy

Teratogenic Effects: *PREGNANCY CATEGORY C:* Reproduction studies performed with mexiletine in rats, mice and rabbits at doses up to four times the maximum human oral dose (24 mg/Kg in a 50 Kg patient) revealed no evidence of teratogenicity or impaired fertility but did show an increase in fetal resorption. There are no adequate and well-controlled studies in pregnant women; this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Mexiletine appears in human milk in concentrations similar to those observed in plasma. Therefore, if the use of mexiletine is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Mexiletine hydrochloride commonly produces reversible gastrointestinal and nervous system adverse reactions but is otherwise well tolerated. Mexiletine has been evaluated in 483 patients in one-month and three-month controlled studies and in over 10,000 patients in a large compassionate use program. Dosages in the controlled studies ranged from 600 to 1200 mg/day; some patients (8%) in the compassionate use program were treated with higher daily doses (1600 to 3200 mg/day). In the three-month controlled trials comparing mexiletine to quinidine, procainamide and disopyramide, the most frequent adverse reactions were upper gastrointestinal distress (41%), lightheadedness (10.5%), tremor (12.6%) and coordination difficulties (10.2%). Similar frequency and incidence were observed in the one-month placebo-controlled trial. Although these reactions were generally not serious, and were dose-related and reversible with a reduction in dosage, by taking the drug with food or antacid or by therapy discontinuation, they led to therapy discontinuation in 40% of patients in the controlled trials. A tabulation of the adverse events reported in the one-month placebo-controlled trial follows:

COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE AND PLACEBO IN THE 4-WEEK, DOUBLE-BLIND CROSSOVER TRIAL

	Mexiletine N=53	Placebo N = 48
Cardiovascular		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmia/PVC's	1.9	—
Digestive		
Nausea/Vomiting/Heartburn	39.6	6.1
Central Nervous System		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	—
Nervousness	11.3	6.1
Coordination Difficulties	9.4	—
Changes in Sleep Habits	7.5	16.3
Paresthesias/Numbness	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2.0
Dyspnea/Respiratory	5.7	10.2
Rash	3.8	2.0
Non-specific Edema	3.8	—

A tabulation of adverse reactions occurring in one percent or more of patients in the three-month controlled studies follows:

COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE OR CONTROL DRUGS IN THE 12-WEEK DOUBLE-BLIND TRIALS

	Mexiletine N = 430	Quinidine N = 262	Procainamide N = 78	Disopyramide N = 69
Cardiovascular				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVC's	1.0	2.7	2.6	—
Digestive				
Nausea/Vomiting/Heartburn	39.3	21.4	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4.0	—	6.4	11.6
Changes in Appetite	2.6	1.9	—	—
Abdominal Pain/ Cramps/Discomfort	1.2	1.5	—	1.4
Central Nervous System				
Dizziness/Lightheadedness	18.9	14.1	14.1	2.9
Tremor	13.2	2.3	3.8	1.4
Coordination Difficulties	9.7	1.1	1.3	—
Changes in Sleep Habits	7.1	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness	5.0	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	—	—
Confusion/Clouded Sensorium	2.6	—	3.8	—
Paresthesias/ Numbness	2.4	2.3	2.6	—
Tinnitus	2.4	1.5	—	—
Depression	2.4	1.1	1.3	1.4
Other				
Blurred Vision/Visual Disturbances	5.7	3.1	5.1	7.2
Headache	5.7	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Dyspnea/Respiratory	3.3	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	—

Less than 1 %: Syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary hesitancy/retention, malaise, impotence/decreased libido, pharyngitis, congestive heart failure.

An additional group of over 10,000 patients has been treated in a program allowing administration of mexiletine hydrochloride under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy. Twenty-four percent of the patients continued in the program for one year or longer. Adverse reactions leading to therapy discontinuation occurred in 15 percent of patients (usually upper gastrointestinal system or nervous system effects). In general, the more common adverse reactions were similar to those in the controlled trials. Less common adverse events possibly related to mexiletine use include:

Cardiovascular System: Syncope and hypotension, each about 6 in 1000; bradycardia, about 4 in 1000; angina/ angina-like pain, about 3 in 1000; edema, atrioventricular block/conduction disturbances and hot flashes, each about 2 in 1000; atrial arrhythmias, hypertension and cardiogenic shock, each about 1 in 1000.

Central Nervous System: Short-term memory loss, about 9 in 1000 patients; hallucinations and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000. Rare cases of severe hepatitis/acute hepatic necrosis.

Skin: Rare cases of exfoliative dermatitis and Stevens-Johnson Syndrome with mexiletine treatment have been reported.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; salivary changes, hair loss and impotence/ decreased libido, each about 4 in 1000; malaise, about 3 in 1000; urinary hesitancy/retention, each about 2 in 1000; hiccups, dry skin, laryngeal and pharyngeal changes and changes in oral mucous membranes, each about 1 in 1000; SLE syndrome, about 4 in 10,000.

Hematology: Blood dyscrasias were not seen in the controlled trials but did occur among 10,867 patients treated with mexiletine in the compassionate use program (see **PRECAUTIONS**).

Myelofibrosis was reported in two patients in the compassionate use program--one was receiving long-term thiotepa therapy and the other had pretreatment myeloid abnormalities.

In postmarketing experience, there have been isolated, spontaneous reports of pulmonary changes including pulmonary fibrosis during mexiletine therapy with or without other drugs or diseases that are known to produce pulmonary toxicity. A causal relationship to mexiletine therapy has not been established. In addition, there have been isolated reports of exacerbation of congestive heart failure in patients with preexisting compromised ventricular function. There have been rare reports of pancreatitis associated with mexiletine treatment.

OVERDOSAGE

Clinical findings associated with mexiletine overdosage have included nausea, hypotension, sinus bradycardia, paresthesia, seizures, bundle branch block, AV heart block, asystole, ventricular tachyarrhythmia, including ventricular fibrillation, cardiovascular collapse and coma. The lowest known dose in a fatality case was 4.4 g with postmortem serum mexiletine level of 34-37 mcg/mL (Jequier P. et al. Lancet 1976; 1 (7956): 429). Patients have recovered from ingestion of 4 g to 18 g of mexiletine (Frank S. E. et al. Am J Emerg Med 1991; 9:43-48).

There is no specific antidote for mexiletine. Management of mexiletine overdosage includes general supportive measures, close observation and monitoring of vital signs. In addition, the use of pharmacologic interventions (e.g., pressor agents, atropine or anticonvulsants) or transvenous cardiac pacing is suggested, depending on the patient's clinical condition.

DOSAGE AND ADMINISTRATION

The dosage of mexiletine hydrochloride must be individualized on the basis of response and tolerance, both of which are dose-related. Administration with food or antacid is recommended. Initiate mexiletine therapy with 200 mg every eight hours when rapid control of arrhythmia is not essential. A minimum of two to three days between dose adjustments is recommended. Dose may be adjusted in 50 or 100 mg increments up or down.

As with any antiarrhythmic drug, clinical and electrocardiographic evaluation (including Holter monitoring if necessary for evaluation) are needed to determine whether the desired antiarrhythmic effect has been obtained and to guide titration and dose adjustment.

Satisfactory control can be achieved in most patients by 200 to 300 mg given every eight hours with food or antacid. If satisfactory response has not been achieved at 300 mg q8h, and the patient tolerates mexiletine well, a dose of 400 mg q8h may be tried. As the severity of CNS side effects increases with total daily dose, the dose should not exceed 1200 mg/day.

In general, patients with renal failure will require the usual doses of mexiletine hydrochloride. Patients with severe liver disease, however, may require lower doses and must be monitored closely. Similarly, marked right-sided congestive heart failure can reduce hepatic metabolism and reduce the needed dose. Plasma level may also be affected by certain concomitant drugs (see **PRECAUTIONS: Drug Interactions**).

Loading Dose: When rapid control of ventricular arrhythmia is essential, an initial loading dose of 400 mg of mexiletine hydrochloride may be administered, followed by a 200 mg dose in eight hours. Onset of therapeutic effect is usually observed within 30 minutes to two hours.

Q12H Dosage Schedule: Some patients responding to mexiletine may be transferred to a 12 hour dosage schedule to improve convenience and compliance. If adequate suppression is achieved on a mexiletine hydrochloride dose of 300 mg or less every eight hours, the same total daily dose may be given in divided doses every 12 hours while carefully monitoring the degree of suppression of ventricular ectopy. This dose may be adjusted up to a maximum of 450 mg every 12 hours to achieve the desired response.

Transferring to Mexiletine hydrochloride: The following dosage schedule, based on theoretical considerations rather than experimental data, is suggested for transferring patients from other Class 1 oral antiarrhythmic agents to mexiletine: Mexiletine hydrochloride treatment may be initiated with a 200 mg dose, and titrated to response as described above, 6 to 12 hours after the last dose of quinidine sulfate, 3 to 6 hours after the last dose of procainamide, 6 to 12 hours after the last dose of disopyramide or 8 to 12 hours after the last dose of tocainide.

In patients in whom withdrawal of the previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, hospitalization of the patient is recommended.

When transferring from lidocaine to mexiletine, the lidocaine infusion should be stopped when the first oral dose of mexiletine hydrochloride is administered. The infusion line should be left open until suppression of the arrhythmia appears to be satisfactorily maintained. Consideration should be given to the similarity of the adverse effects of lidocaine and mexiletine and the possibility that they may be additive.

HOW SUPPLIED

Mexiletine Hydrochloride Capsules are supplied in hard gelatin capsules containing 150 mg, 200 mg or 250 mg of mexiletine hydrochloride.

Mexiletine hydrochloride capsules, brown opaque cap and light brown opaque body, imprinted with WATSON 491 and 150 mg are supplied in bottles of:

100, NDC 52544-491-01
500, NDC 52544-491-05

Mexiletine hydrochloride capsules, brown opaque cap and body, imprinted with WATSON 492 and 200 mg are supplied in bottles of:

100, NDC 52544-492-01
500, NDC 52544-492-05

Mexiletine hydrochloride capsules, brown opaque cap and light green opaque body, imprinted with WATSON 493 and 250 mg are supplied in bottles of:

100, NDC 52544-493-01
500, NDC 52544-493-05

Store below 30°C (86°F)
Caution: Federal law prohibits dispensing without prescription.

WATSON LABORATORIES, INC
Corona, California 91720

Revised December 11, 1996
13073-1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074711

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA #74-711

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc.
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, CA 91720

4. LEGAL BASIS FOR SUBMISSION
Mexitil Capsules; Boehringer Ingelheim. Patent expired on May 04, 1995 and no expiration date for exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Mexiletine Hydrohloride Capsules, USP

7. NONPROPRIETARY NAME
Mexiletine Hydrohloride Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firms:
July 14, 1995: Original submission
May 29, 1996: Amendment
January 7, 1997: Minor Amendment
January 21, 1997: Telephone call

FDA:
August 09, 1995: Acknowledgement letter
February 29, 1996: Deficiency letter
December 2, 1996: Minor Deficiency letter
February 3, 1997: Telephone amendment

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Oral Capsule

14. POTENCY
150 mg, 200 mg and 250 mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074711

BIOEQUIVALENCE REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 74-711

Food and Drug Administration
Rockville MD 20857

JUN 26 1996

Watson Laboratories, Inc.
Attention: Dr. David C. Hsia
311 Bonnie Circle
Corona, CA 91720

Dear Dr. Hsia:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Mexiletine Hydrochloride Capsules, 150 mg, 200 mg, and 250 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 ml of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test drug product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 18 1996

Mexiletine Hydrochloride
150, 200, 250 mg capsules
ANDA #74-711
Reviewer: James D. Henderson
File: 74711SDW.296

Watson Laboratories
Corona, CA
Submitted:
February 6, 1996

RESPONSE TO REVIEW OF FASTING AND FED BIOEQUIVALENCE STUDIES

BACKGROUND:

1. On 7/14/95 the sponsor submitted the results of fasting and fed bioequivalence studies of its test product mexiletine hydrochloride 250 mg capsules compared to the reference listed drug (RLD) Mexitil® (NDA #18-873, approved 12/30/85, Boehringer Ingelheim, BI). Waiver of in vivo demonstration of bioequivalence was requested for the two lower strengths 200 mg and 150 mg capsules based on formula proportionality and dissolution testing.

2. The submission was reviewed and found incomplete (12/20/95) with deficiencies. The sponsor was informed of the deficiency comments in a letter of 1/18/96. The present submission is a response to the deficiency comments.

RESPONSES TO DEFICIENCY COMMENTS:

(Note: Deficiency comments are numbered as they appeared in the 1/18/96 letter.)

1. Deficiency comment #1a

Reviewer's Comment: Acceptable.

2. Deficiency comment #1b

Reviewer's Comment: Acceptable (see Table 1).

3. Deficiency comment #2

Reviewer's Comment: Acceptable.

4. Deficiency comment #3

Reviewer's Comment: Acceptable.

5. Deficiency comment #4

Reviewer's Comment: Acceptable.

ADDITIONAL COMMENTS:

1. On checking some of the AUC0-t values, the reviewer noted some discrepancies between calculated and reported results. Therefore, the reviewer recalculated all the AUC0-t values using the data from Tables 4.5.1 and 4.5.2 in the original submission and compared the results to the reported values in Tables 4.5.3 and 4.5.4. In six cases (T 1, R 5) the values recalculated by the reviewer differed from the reported values by -0.04% to -0.63%. These differences may be attributable to rounding errors or to using exact sampling times not given in the tables. These small degrees of difference are not expected to affect the study outcome.

2. The fed study was conducted as a two-way crossover design comparing the test and reference products under fed conditions. There is no DBE guidance for mexiletine hydrochloride, and the exclusion of the test fasting treatment is not required for bioequivalence determination. Therefore, the reviewer recommends that this study be accepted.

CONCLUSIONS:

1. The deficiency comments have been answered successfully and the fasting and fed studies are acceptable.

2. Based on exact formula proportionality and acceptable dissolution data, the requests for waiver of in vivo studies for the 150- and 200-mg strengths may be granted.

RECOMMENDATIONS:

1. The bioequivalence study (fasting conditions) conducted by Watson Laboratories on its mexiletine hydrochloride 250 mg capsule, lot #R51494, comparing it to Mexitil® 250 mg capsule, lot #683002A, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Watson's mexiletine hydrochloride 250 mg capsule is bioequivalent under fasting conditions to the reference product Mexitil® 250 mg capsule manufactured by Boehringer Ingelheim (BI).

2. The bioequivalence study (fed conditions) conducted by Watson Laboratories on its mexiletine hydrochloride 250 mg capsule, lot #R51494, comparing it to Mexitil® 250 mg capsule, lot #683002A, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Watson's mexiletine hydrochloride 250 mg capsule is bioequivalent under fed conditions to the reference product Mexitil® 250 mg capsule manufactured by Boehringer Ingelheim (BI).

3. The dissolution testing conducted by Watson on its mexiletine hydrochloride 250 mg capsule, lot #R51494, is acceptable and should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. The dissolution testing conducted by Watson on its mexiletine hydrochloride 200 mg capsule, lot #R51394, and 150 mg capsule, lot #R51294, is acceptable. The firm has conducted acceptable in vivo bioequivalence studies under fasting and fed conditions (submitted 7/14/95 and 2/6/96) comparing its 250 mg capsule of

the test product with the 250 mg capsule of the reference product Mexitil® manufactured by BI. The formulations for the 200 mg and 150 mg strengths are proportionally similar with respect to active and inactive ingredients to the 250 mg strength of the test product that underwent bioequivalency testing. The waivers of in vivo bioequivalence study requirements for the 200 mg and 150 mg strengths of the test product are granted. The 200 mg and 150 mg capsules of the test product are therefore deemed bioequivalent to the 200 mg and 150 mg capsules, respectively, of Mexitil® manufactured by BI.

5. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is acceptable.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

6/17/1996

Concur: _____ Date 6/18/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

JDH/gj/6-17-96/74711

cc: ANDA #74-711 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): mexiletine hydrochloride
Dose Strength: 250 , 200, and 150 mg capsules
ANDA No.: 74-711
Firm: Watson
Submission Date: 2/6/96
File Name: 74711SDW.296

I. Dissolution Testing (USP Method):

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: water Volume: 900 mL
Specifications: NLT 30 min
Reference Drug: Mexitil® (BI)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product mexiletine HCl Lot #R51494 (tested 12/16/94) Strength (mg) 250			Reference Product Mexitil® Lot #683002A (tested 1/14/95) Strength (mg) 250 exp 7/96		
	Mean %	Range	%CV	Mean %	Range	%CV
5	42.6		28.1	65.2		9.4
10	78.8		12.5	84.6		6.2
20	92.5		4.8	94.0		3.9
30	96.1		3.6	97.0		2.7
Sampling Times (Minutes)	Test Product mexiletine HCl Lot #R51394 (tested 5/18/95 Strength (mg) 200			Reference Product Mexitil® Lot #675001A (tested 5/13/95) Strength (mg) 200 exp 1/98		
	Mean %	Range	%CV	Mean %	Range	%CV
5	46.7		31.6	65.3		17.9
10	82.2		14.9	87.3		10.0
20	96.2		6.8	96.7		3.4
30	99.7		3.7	99.7		2.2
Sampling Times (Minutes)	Test Product Lot #R51294 (tested 5/18/95) Strength (mg) 150			Reference Product Mexitil® Lot #664018A (tested 5/13/95) Strength (mg) 150 exp 1/98		
	Mean %	Range	%CV	Mean %	Range	%CV
5	60.3		20.4	62.4		16.8
10	87.6		7.3	88.6		7.7
20	96.8		3.4	96.8		3.5
30	99.9		2.4	99.1		2.4

DEC 2 0 1995

Mexiletine Hydrochloride
150, 200, 250 mg capsules
ANDA #74-711
Reviewer: James D. Henderson
File: 74711SDW.795

Watson Laboratories
Corona, CA
Submitted:
July 14, 1995

REVIEW OF FASTING AND FED BIOEQUIVALENCE STUDIES AND WAIVER REQUESTS

The sponsor has submitted the results of fasting and fed bioequivalence studies of its test product mexiletine hydrochloride 250 mg capsules compared to the reference listed drug (RLD) Mexitil® (NDA #18-873, approved 12/30/85, Boehringer Ingelheim, BI). Waiver of in vivo demonstration of bioequivalence is requested for the two lower strengths 200 mg and 150 mg capsules. Patent expiration for the RLD is on 5/4/95.

BACKGROUND[1]

Mexitil® is a local anesthetic, orally active antiarrhythmic agent (Class 1B) structurally similar to lidocaine. It is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Mexitil® is currently available as 150, 200, and 250 mg capsules.

Mexitil® is well absorbed (≈ 90%) from the GI tract with low first-pass metabolism. Time to peak blood levels (TMAX) is 2-3 hours. The plasma elimination half-life is about 10-12 hours. Hepatic metabolism results in a metabolite N-methylmexiletine which is about 20% as potent as the parent drug in animal models. The urinary excretion of unchanged mexiletine and N-methylmexiletine is about 10% and < 0.5%, respectively. From these results, the therapeutic activity of mexiletine is due to the parent compound.

The labeling states that "The dosage of Mexitil® must be individualized on the basis of response and tolerance, both of which are dose-related. Administration with food or antacid is recommended". Therapy may be initiated with 200 mg every 8 hours when rapid control is not necessary. Satisfactory control is usually achieved with 200-300 mg every 8 hours when the drug is given with food or antacid. The total daily dose should not exceed 1200 mg.

FASTING STUDY

I. Study Design

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[1] PDR, 49th ed., 1995, p. 640-3

This was a single dose, randomized, two-way crossover bioequivalence study comparing equal doses (250 mg) of the test product mexiletine hydrochloride 250 mg capsules (Watson) with the RLD Mexitil® 250 mg capsules (BI) in healthy male subjects under fasting conditions with at least one week washout between the two study periods. Plasma concentrations of mexiletine were measured.

II. Study Site

Clinical Site:
Medical Director:
Scientific Director:
Protocol #: B-11304, 11/30/94 (IRB approval 3/9/95)
Study #: B-11304
Study Dates: Period I dosing on 3/11/95; Period II dosing on 3/18/95
Analytical Site:
Analytical Director:
Analysis Dates: 4/1-4/24/95 (44 days frozen storage)

III. Subject Selection

Twenty-six subjects were enrolled (no alternates) and 24 subjects completed both study phases:

Sequence 1: Subjects 1,5,6,7,9,11,13,15,17,18,23,24,26
Sequence 2: Subjects 2,3,4,8,10,12,14,16,19,20,21,22,25

A. Inclusion Criteria

- male, 18-45 years old
- weight range of 135-246 pounds and within ± 10% of ideal weight for height (Metropolitan Life Insurance Company Statistical Bulletin, 1983)
- good health as determined by medical history, physical examination, and laboratory tests
- clinical lab values > 20% outside the normal range may be retested; if still outside the normal range, the subject may not participate unless the clinical director deems the result as clinically insignificant

B. Exclusion Criteria

- history of or ongoing serious organ, systemic, or psychiatric disease
- history of chronic alcohol consumption or drug addiction
- history of allergic responses to the drug class being studied
- tobacco smoking
- positive urine drug screen at check-in prior to each phase
- blood donation, consumption of any investigational drug, or exposure to known enzyme inducing or inhibiting agents within one

month of study start

IV. Study Procedures

Both treatments were administered with 240 mL of water, and a mouth check was performed to assure ingestion. There was a 7-day washout period between doses.

A. Treatments

1) Trt. A (test), mexiletine hydrochloride 250 mg capsules, dose = 250 mg (1 capsule), Watson lot #R51494, potency 101.1%; manufactured 12/16/94, theoretical batch size actual yield,

2) Trt. B (RLD), Mexitil® 250 mg capsule, dose = 250 mg (1 capsule), BI lot #683002A (exp 7/96), potency 98.3%

B. Restrictions

Subjects were confined at the clinical site from 10 hours before dosing until 24 postdose, and instructed to return for the 36- and 48-hour samples. No medications (including OTC) were allowed for two weeks prior to study start. Alcohol and caffeine- or xanthine-containing products were prohibited from 48 hours prior to dosing in both periods and during the sample collection intervals.

C. Meals and Fluids

Fasting occurred for at least 10 hours predose until four hours postdose when standardized meals were begun. Water was allowed freely except within one hour predose and two hours postdose. No caffeine-containing food or drinks were allowed at the clinical facility.

D. Blood Sampling

Venous blood (10 mL) samples were collected in EDTA-Vacutainers® at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours postdose. Samples were centrifuged at 3400 rpm for 15 min and the plasma was separated and stored frozen in labeled tubes at -20° pending assay. Samples were shipped to the analytical site and received in frozen condition with ample dry ice remaining.

E. Monitoring

BP and pulse rate were measured at 0 (predose), 2, 4, 6, 12, and 24 hours postdose.

V. Analytical Methodology

VI. Data Analysis

A. Pharmacokinetic Calculations

- AUC0-T, trapezoidal rule, to last nonzero concentration C(T)
- AUCINF, AUC0-T + C(T)/KE
- KE, estimated by linear least squares regression of the terminal data points
- HL, log(2)/KE
- CMAX and TMAX, from observed data

B. Statistical Analysis

Log-transformed data was subjected to ANOVA (SAS v. 6.10 GLM procedure) using a statistical model with terms for sequence, subjects within sequence, period, and treatment. The 90% confidence intervals (CI) were calculated as part of the Two One-Sided Tests procedure.

VII. Results

A. Product Information

1. Formulation of the test product: Table 1

2. Dissolution: Table 2

3. Potencies: within ± 5%

B. Clinical

1. Completion:

Twenty-four subjects completed the crossover. S3 dropped from the study prior to Period 2 due to a scheduled job interview. S13 dropped from the study prior to Period 2 due to a work-related injury and need for subsequent medications.

2. Protocol Deviations:

a. early/late blood sampling

There were 11 late samples, nine of these occurring at the 36- or 48-hr draw and ranging from 5-51 minutes late. Corrections were made in the PK parameter calculations for the deviations from target times.

b. missing samples

There were two missing samples: S11, Per.1, 4 hr, "poor condition" (frothy, much lighter color), and S15, Per. 1, 8 hr, no-show.

3. Adverse Events: none

C. Pharmacokinetics/Statistics

1. Mean plasma mexiletine concentrations from the test product and RLD are shown in Table 3. There were no reported predose concentrations or instances of CMAX as the first nonzero concentration.

2. Mean reported pharmacokinetic parameters for mexiletine are shown in Table 4. There were no statistically significant period ($p > 0.05$) or sequence ($p > 0.1$) effects noted for log-transformed AUC0-t, AUCINF, or CMAX. There were statistically significant treatment effects ($p < 0.05$) for CMAX and logCMAX.

3. T/R ratios are shown in Table 5.

D. Analytical

2. prestudy validation: Table 6

VIII. Comments

1. Using the diskette data supplied by the sponsor, the reviewer repeated the data analysis with the GLM procedure of SAS and confirmed the sponsor's results for 90% CI's of log-transformed AUC0-t, AUCINF, and CMAX.

2. The reviewer calculated additional pharmacokinetic parameters: RATIO (=AUC0-t/AUCINF); DURATION (=TLAST/HALF) where TLAST is the time of the last quantifiable concentration; WASHOUT (=168/HALF). Only one value of RATIO was < 0.8 (S16, Trt. B) and the mean values for both treatments were > 0.9. Five values of DURATION were in the range 2.5-3 half-lives. All values of WASHOUT were > 7 half-lives.

8. Twenty-eight samples were listed as reassayed for the following reasons: chromatographic interference (14), predose peak (5), sample not received (1), anomalous value (7), value above range (1).

- For 6 of the 7 anomalous values, the median value (original, repeat1, repeat2) was reported; in 5 cases the median was one of the repeat values. The 7th anomalous value was S11, Per. 1, 4-hr reported as "missing".

- Five samples were reassayed as "peak in 0 hour" with no original value and only one repeat value (which was the value reported). Sample 10, Per. 1, had a repeat1 value of 58.1 and a value used of 58.1. However, Table 4.5.2 reports a value of 0 for this sample.

FED STUDY

I. Study Design

This was a single dose, randomized, two-way crossover bioequivalence study comparing equal doses (250 mg) of the test product mexiletine hydrochloride 250 mg capsules (Watson) with the RLD Mexitil® 250 mg capsules (BI) in healthy male subjects under fed conditions with at least one week washout between the two study periods. Plasma concentrations of mexiletine were measured.

II. Study Site

Clinical Site:
Medical Director:
Scientific Director:
Protocol #: B-05283, 12/20/94 (IRB approval 1/16/95)
Study #: B-05283
Study Dates: Period I dosing on 1/22/95); Period II dosing on 1/29/95
Analytical Site:
Analytical Director:
Analysis Dates: 2/28-3/16/95 (53 days frozen storage)

III. Subject Selection

Twenty-six subjects were enrolled (no alternates) and 25 subjects completed both study phases:

Sequence 1: Subjects 1,2,5,9,10,13,14,15,18,21,22,23,24

Sequence 2: Subjects 3,4,6,7,8,11,12,16,17,19,20,25,26

Inclusion and exclusion criteria were the same as for the fasting study. Plasma samples from 25 subjects were assayed for mexiletine.

IV. Study Procedures

Both treatments were administered with 240 mL of water, and a mouth check was performed to assure ingestion. There was a 7-day washout period between doses.

- Treatments

1) Trt. A (test), mexiletine hydrochloride 250 mg capsules, dose = 250 mg (1 capsule), Watson lot #R51494

2) Trt. B (RLD), Mexitil® 250 mg capsule, dose = 250 mg (1 capsule), BI lot #683002A (exp 7/96)

Thirty minutes before each dosing subjects were served a standard breakfast consisting of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180 mL of orange juice, and 240 mL of whole milk. Subjects finished the entire meal within 30 minutes.

- Restrictions, Meals and Fluids, Blood Sampling, and Monitoring were the same as for the fasting study.

V. Analytical Methodology

VI. Data Analysis

A. Pharmacokinetic Calculations

- AUC0-T, trapezoidal rule, to last nonzero concentration C(T)
- AUCINF, AUC0-T + C(T)/KE
- KE, estimated by linear least squares regression of the terminal data points
- HL, log(2)/KE
- CMAX and TMAX, from observed data

B. Statistical Analysis

Log-transformed data was subjected to ANOVA (SAS v. 6.10 GLM procedure) using a statistical model with terms for sequence, subjects within sequence, period, and treatment. The 90% confidence intervals (CI) were calculated as part of the Two One-Sided Tests procedure.

VII. Results

A. Clinical

1. Completion:

Of the 26 subjects enrolled, 25 subjects completed the crossover. Subject #21 dropped from the study prior to Period 2 due to personal reasons.

2. Protocol Deviations:

a. blood sampling

There were 13 late samples and 2 early samples, 14 of these occurring at the 36- or 48-hr draw and ranging from 5-351 minutes late. Corrections were made in the PK parameter calculations for the deviations from target times.

3. Adverse Events:

Trt. A: There were 3 events (nausea, emesis) involving 1 subject (S25) of mild to moderate severity, judged as possibly due to the drug. No therapy was required.

Trt. B: There were 4 events involving 1 subject (S6) of mild to moderate severity (nausea, emesis, diaphoresis), judged as possibly due to the drug. No therapy was required.

B. Pharmacokinetics/Statistics

1. Mean plasma mexiletine concentrations from the test product and RLD are shown in Table 8. There were no reported predose concentrations or instances of CMAX as the first nonzero concentration.

2. Mean reported pharmacokinetic parameters for mexiletine are

shown in Tables 9 and 10. There were no statistically significant period ($p > 0.05$) or sequence ($p > 0.1$) effects noted for log-transformed AUC0-t, AUCINF, or CMAX. There were statistically significant treatment effects ($p < 0.05$) for CMAX and logCMAX.

C. Analytical

VIII. Comments

1. Using the diskette data supplied by the sponsor, the reviewer repeated the data analysis with the GLM procedure of SAS and confirmed the sponsor's results for ratios and 90% CI's of log-transformed AUC0-t, AUCINF, and CMAX.

2. The reviewer calculated additional pharmacokinetic parameters: RATIO (=AUC0-t/AUCINF), and WASHOUT (=168/HALF). All values of RATIO were < 0.8 and the mean values for both treatments were > 0.9. All values of WASHOUT were > 7 half-lives.

6. Fifteen samples were listed as reassayed for the following reasons: chromatographic interference (5), instrument malfunction (1), anomalous value (8), value above range (1). For all anomalous values, the median value (original, repeat1, repeat2) was reported, and the median was one of the repeat values.

WAIVER REQUESTS

1. The sponsor has requested waiver of in vivo study requirements for its mexiletine hydrochloride 200 mg and 150 mg capsules. In accordance with 21 CFR 320.22(d)(2), the sponsor states:

- composition of the capsules is similar

From Table 1, the ratios of the amounts of core excipients between the 250 mg and 200 mg capsule are exactly the same as for the active ingredient. Similarly, the ratios of the amounts of core excipients between the 250 mg and 150 mg capsule are exactly the same as for the active ingredient. Therefore, the three formulations are exactly proportional.

- dissolution data is similar for both products

USP 23, p. 1024, states the following dissolution conditions and specification for mexiletine hydrochloride capsules: water, 900 mL, apparatus 2, 50 rpm, NLT 30 minutes. The sponsor used these same conditions. The dissolution testing results are acceptable for all three strengths.

2. The biostudies for the 250 mg strength capsule have deficiencies as stated below.

DEFICIENCIES

Applicable to both studies:

1. The absolute recovery data should be repeated using a minimum of six extracted samples and six unextracted samples at each of at least two concentrations in order to obtain a meaningful coefficient of variation (CV).

2. The coefficients of variation (CV%) must be calculated for each dissolution sampling time for all strengths of both test and reference products.

Applicable to the fasting study

3. According to the reassay list (Table 8.3, p. 8-7), Subject 10, Per. 1, predose sample, had a repeat1 value of 58.1 and a value used of 58.1. However, Table 4.5.2 reports a value of 0 for this sample. Please explain.

Applicable to the fed study:

4. The protocol specifies that the entire standard breakfast was to be consumed within the 30 minutes prior to dosing. The sponsor should verify that all subjects consumed the entire breakfast in the allotted time since this is not specifically indicated in the Case Report Forms.

RECOMMENDATIONS

1. The bioequivalence study (fasting conditions) conducted by Watson Laboratories on its mexiletine hydrochloride 250 mg capsule, lot #R51494, comparing it to Mexitil® 250 mg capsule, BI lot #683002A, has been found incomplete by the Division of Bioequivalence due to deficiencies #1-3.

2. The bioequivalence study (fed conditions) conducted by Watson Laboratories on its mexiletine hydrochloride 250 mg capsule, lot #R51494, comparing it to Mexitil® 250 mg capsule, BI lot #683002A, has been found incomplete by the Division of Bioequivalence due to deficiencies #1,2, and 4.

3. The sponsor should be informed of deficiency comment #1-4 and recommendations #1-2.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

Concur 12/12/95

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

JDH/gj/12-18-95/74711

cc: ANDA #74-711 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

Table 1 - Formulations of the Test Products

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Ingredient	150 mg	200 mg	250 mg
CORE		mg/capsule	
mexiletine hydrochloride, USP	150	200	250
pregelatinized starch, NF			
colloidal silicon dioxide, NF			
corn starch, NF			
magnesium stearate, NF			
sodium lauryl sulfate, NF			
CAPSULE			
black iron oxide			
red iron oxide			
yellow iron oxide			
FD&C Blue #1			
D&C Yellow #10			
FD&C Red #40			
D&C Red #28			
titanium dioxide			
FD&C Green #3			

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): mexiletine hydrochloride
Dose Strength: 250 , 200, and 150 mg capsules
ANDA No.: 74-711
Firm: Watson
Submission Date: 7/14/95
File Name: 74711SDW.795

I. Dissolution Testing (USP Method):

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: water Volume: 900 mL
Specifications: NLT 30 min
Reference Drug: Mexitil® (BI)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product mexiletine HCl Lot #R51494 (tested 12/16/94) Strength (mg) 250			Reference Product Mexitil® Lot #683002A (tested 1/14/95) Strength (mg) 250 exp 7/96		
	Mean %	Range	%CV	Mean %	Range	%CV
5	42.6		-	65.2		-
10	78.8		-	84.6		-
20	92.5		-	94.0		-
30	96.1		-	97.0		-

Sampling Times (Minutes)	Test Product mexiletine HCl Lot #R51394 (tested 5/18/95 Strength (mg) 200			Reference Product Mexitil® Lot #675001A (tested 5/13/95) Strength (mg) 200 exp 1/98		
	Mean %	Range	%CV	Mean %	Range	%CV
5	46.7		-	65.3		-
10	82.2		-	87.3		-
20	96.2		-	96.7		-
30	99.7		-	99.7		-

Sampling Times (Minutes)	Test Product Lot #R51294 (tested 5/18/95) Strength (mg) 150			Reference Product Mexitil® Lot #664018A (tested 5/13/95) Strength (mg) 150		
	Mean %	Range	%CV	Mean %	Range	%CV
5	60.3		-	62.4		-
10	87.6		-	88.6		-
20	96.8		-	96.8		-
30	99.9		-	99.1		-

Table 3 - Mean Reported Plasma Mexiletine Concentrations (ng/mL, Fasting Study, N = 24)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) cv(%)	% Diff.
0	0.00	-	0.00	-	-
0.5	19.775	114	40.462	115	-51.1
1	212.42	39	226.97	40	-6.41
1.5	298.5	23	334.71	26	-10.8
2	351.88	19	367.12	21	-4.15
2.5	361.5	17	391.21	21	-7.59
3	369.38	18	383.25	19	-3.62
4	353.91	22	358.42	22	-1.26
5	310.04	20	323.17	26	-4.06
6	291.5	23	289.08	25	0.837
8	257.54	29	264.08	26	-2.48
12	189.9	35	184.85	34	2.732
16	148.25	47	143.35	45	3.418
24	95.063	65	95.046	31	0.018
36	41.433	107	39.362	95	5.261
48	17.561	134[1]	17.817	145	-1.44

[1] N = 23

Trt. A = mexiletine hydrochloride 250 mg capsule, Watson
Trt. B = Mexitil® 250 mg capsule, BI

Table 4 - Mean Reported Pharmacokinetic Parameters for Mexiletine (N = 24, Fasting Study)

Parameter[1]	Trt. A (mean)[2]	test CV(%)	Trt. B (mean)	ref. CV(%)	[3]	90% CI
AUC0-T	5872.87	42	5932.75	39	-1.01	95.3-103
logAUC0-T	-	-	-	-	0.979	94.0-102
AUCINF	6432.61	44	6460.57	45	-0.43	95.4-104
logAUCINF	-	-	-	-	0.992	95.3-103
CMAX	394.667	18	415.375	20	-4.99	91.1-99
logCMAX	-	-	-	-	0.953	91.8-99.1
TMAX (hr)	3.229	45	2.563	33	25.99	-
KEL (hr^{-1})	0.074	30	0.075	30	-1.33	-
HALF (hr)	10.214	31	10.179	37	0.344	-

[1] units: AUC, ng*hr/mL; CMAX, ng/mL

[2] Arithmetic and least squares (LSM) means are identical for this balanced study. LSM are reported for AUC's and CMAX; arithmetic means are reported for the other parameters.

[3] For untransformed data, the % difference is calculated as $(A_{mean} - B_{mean})*100/B_{mean}$. For log-transformed values, the ratio of least squares geometric means is reported as exp(ESTIMATE) where the ESTIMATE is obtained from the ANOVA.

Trt. A = mexiletine hydrochloride 250 mg capsule, Watson
Trt. B = Mexitil® 250 mg capsule, BI

Table 5 - T/R Ratios

Subject	AUC0-T	AUCINF	CMAX
1	[illegible]	[illegible]	[illegible]
2			
4			
5			
6			
7			
8			
9			
10			
11			
12			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
< 75%	0	0	1
75-125%	23	24	23
> 125%	1	0	0

Table 6 - Prestudy Validation

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Table 7 - Additional PK Parameters (Fasting Study)

Parameter	Trt. A	CV(%)	Range	Trt. B	CV(%)	Range
RATIO	0.9183	5.2	0.807-0.977	0.9304	4.9	0.765-0.980
DURATION	3.944	22.9	2.5-5.68	4.160	19.6	2.06-5.80
WASHOUT	17.94	29.5	10.1-31.4	18.24	29.8	7.2-30.3

Trt. A = mexiletine hydrochloride 250 mg capsule, Watson
Trt. B = Mexitil® 250 mg capsule, BI

Table 8 - Mean Reported Plasma Mexiletine Concentrations (ng/mL, Fed Study, N = 25)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) cv(%)	% Diff.
0	0.00	-	0.00	-	-
0.5	10.068	352	0.424	500	2275
1	53.976	202	40.684	145	32.67
1.5	114.79	94	111.19	91	3.238
2	215.40	48	187.33	54	14.98
2.5	287.12	34	260.68	31	10.14
3	343.68	21	331.36	22	3.718
4	374.40	22	358.20	19	4.523
5	339.88	21	339.80	24	0.024
6	304.20	26	303.20	22	0.33
8	257.80	28	266.36	29	-3.21
12	197.91	39	195.57	35	1.197
16	148.20	38	149.90	41	-1.13
24	85.368	51	89.812	51	-4.95
36	32.856	68	36.684	77	-10.4
48	11.564	97	12.892	117	-10.3

Trt. A = mexiletine hydrochloride 250 mg capsule, Watson
Trt. B = Mexitil® 250 mg capsule, BI

Table 9 - Mean Reported Pharmacokinetic Parameters for Mexiletine (N = 25, Fed Study)

Parameter[1]	Trt. A (mean)[2]	test CV(%)	Trt. B (mean)	ref. CV(%)	% Diff.[3]
AUC0-T	5515.4	35	5573.32	36	-1.04
AUCINF	5770.96	34	5862.88	38	-1.57
CMAX	402.04	18	379.56	19	5.923
TMAX (hr)	3.52	24	3.84	22	-8.33
KEL (hr^{-1})	0.0786	18	0.0793	22	-0.88
HALF (hr)	9.0616	16	9.1716	23	-1.2

[1] units: AUC, ng*hr/mL; CMAX, ng/mL
[2] Arithmetic means are reported for all parameters.
[3] The % difference is calculated as $(A_{mean} - B_{mean})*100/B_{mean}$.

Table 10 - Least Squares Means (LSM), Ratios, and 90% CI (N = 25, Fed Study)

Parameter[1]	Trt. A (LSM)	Trt. B (LSM)	Ratio[2]	90% CI
AUC0-T	5507.045	5566.061	0.989	96.4-102
logAUC0-T	-	-	0.994	96.7-102
AUCINF	5761.747	5852.234	0.985	95.3-102
logAUCINF	-	-	0.993	96.3-102
CMAX	402.18	380.151	0.918	81.8-102
logCMAX	-	-	1.06	103-109

[1] units: AUC, ng*hr/mL; CMAX, ng/mL
[2] For untransformed data, the ratio is calculated as A_{LSM}/B_{LSM}. For log-transformed values, the ratio of least squares geometric means is reported as exp(ESTIMATE) where the ESTIMATE is obtained from the ANOVA.

Trt. A = mexiletine hydrochloride 250 mg capsule, Watson
Trt. B = Mexitil® 250 mg capsule, BI

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Requestor:
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GAITHERSBURG MD 20878-1703

Request Date:
FDA Recd Date: 09-MAY-1997
CDER Recd Date: 12-MAY-1997
Due Date: 23-MAY-1997

Request Type: COMMERCIAL

CDER Subject:
ROXANE LABS - MEPERIDINE HCL SBA, APRVL LTR, LABELING ETC

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Office		Date Assigned	Status
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